REMARKS

A check for the fee for a one month extension of time accompanies this response. Any additional fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 50-1213.

Claims 32, 35, 38, 39, 65, 82, 83, 87, 97-100 and 106-112 are presently pending in this application. Claims 32, 82 and 109 are amended in order to more particularly point out and distinctly claim the subject matter. Claim 106 is amended to correct minor typographical errors. Claims 111 and 112 have been added. Basis for amendment of Claims 32, 82 and 109 and for adding new Claims 111 and 112 may be found in the specification as originally filed, for example, at page 34, lines 15-24; Example 14 beginning at page 106; page 109, lines 13-23; page 110, lines 1-27; and page 111, lines 1-18. No amendments have been made to obviate prior art and no new matter has been introduced.

A Supplemental Information Disclosure Statement also is filed on the same day herewith under separate cover.

CLAIMS 106 AND 107

Although the Office Action states that all of the pending claims are rejected, no explicit rejection of Claims 106 and 107 is set forth. Rejection of Claim 106 (and Claim 107, which depends on Claim 106) may be implied from the Examiner's mention of Claim 106 (*see* page 4, line 5 of the Office Action) in the discussion supporting the rejection of Claims 32, 35, 38, 39, 65, 82, 83, 87 and 97-100 under 35 U.S.C. §112, first paragraph, for lack of enablement. Nonetheless, Applicant requests clarification of the status of Claims 106 and 107. It is noted, however, that regardless of the status of Claims 106 and 107, Applicant's traversal of the rejection of Claims 32, 35, 38, 39, 65, 82, 83, 87 and 97-100

under 35 U.S.C. §112, first paragraph (*see* below) is also applicable to any claims that have not been so rejected, including Claims 106 and 107.

THE REJECTION OF CLAIMS 32, 35, 38, 39, 65, 82, 83, 87, and 97-100 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 32, 35, 38, 39, 65, 82, 83, 87 and 97-100 are rejected under 35 U.S.C. §112, first paragraph, because it is alleged that while the specification is enabling for a method of producing a transgenic non-human mammal comprising: introducing a cell comprising a satellite artificial chromosome, wherein the cell develops into an embryo in a female non-human mammal *of the same species*, and allowing the embryo to develop into a transgenic non-human mammal comprising the satellite artificial chromosome, the specification does not provide reasonable enablement wherein the cell develops into an embryo in a female non-human mammal *of any species*.

It is alleged that the claims encompass the implantation of embryos into surrogate mothers of different species, the state of the art of which is unpredictable. To support this allegation, the Office Action cites Fehilly *et al.*, which allegedly shows that the generation of animals by implantation into surrogate mothers of a foreign species is an unpredictable process. In view of the state of the art, it is alleged that it would have required undue experimentation for one skilled in the art to make or use the claimed invention.

This rejection is respectfully traversed. It is further respectfully submitted that as discussed above, this traversal is applicable to Claims 106-110. Claims 111 and 112 are outside the purview of the rejection.

It also is noted that, while the rejection of independent Claim 82 and Claims 83 and 87, which are dependent thereon, is traversed herein, these claims also appear to be outside the purview of this rejection because these claims, directed to a method of producing a transgenic embryo by introducing a satellite artificial chromosome into a cell and culturing the cell under conditions where it develops into an embryo, do not recite a step of implantation of the embryo into surrogate mothers.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971) (emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant specifically has exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

The Examiner urges that "the specification does not reasonably provide enablement . . . wherein the cell develops into an embryo in a female non-human mammal *of any species*." (emphasis added) The basis for this allegation is that the implantation of embryos into surrogate mothers of different species is unpredictable. To support this allegation, the Examiner cites Fehilly *et al.* (1984) *Nature* 307:634-636 as an example of the unpredictability of implantation of embryos from foreign species into a surrogate mother. It is alleged that Fehilly *et al.* teaches that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as placental abnormalities and maternal immunological reactions in interspecific pregnancies.

As discussed below, this rejection is improper and is traversed on several bases. 1) The standard for enablement is whether it would require undue experimentation to practice the method as claimed, not whether there is "reasonable enablement" as recited by the Examiner. In particular, the inquiry with respect to scope of enablement is not limited to a consideration of predictability. Predictability is just one of about nine factors that are considered. 2) Second, the basis for the Examiner's conclusion that the process is unpredictable is incorrect; the cited article and the state of the art, particularly in light of the instant

disclosure, does not warrant a conclusion that the process of introducing an embryo from one species into a host from another species is unpredictable. 3) Third, consideration of the factors that should be considered leads to the conclusion that it would not require undue experimentation to practice the methods as claimed. 4) Finally, it is would be unfair and unduly limiting to limit the claims as proposed by the Examiner.

1) The inquiry with respect to scope of enablement is **not** limited to a consideration of predictability

The Examiner alleges that in view of the state of the art with regard to the unpredictability of implantation of embryos from foreign species into a surrogate mother, it would have required undue experimentation for one of skill in the art to make and/or use the claimed subject matter.

Applicant respectfully submits that predictability is only one factor to be considered in an analysis of whether the level of experimentation required is undue. Unpredictability does not equate with a lack of enablement. The requisite inquiry to assess whether a claim is enabled includes additional factors: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). While not conceding that there is evidence in support of the unpredictability of the instantly claims methods (discussed below), the Examiner has improperly used "unpredictability" alone as the basis for rejecting the instant claims on the grounds of lack of enablement.

As discussed below, a consideration of the level of skill in the art as of the effective filing date of the instant application, the knowledge of those of skill in the art, the teachings and disclosure in the specification, and the predictability of the art leads to the conclusion that undue experimentation is not required to perform

the methods of the instant application where the species of the surrogate and embryo differ.

Further, the claims need not be enabled for the implantation of *any and all species* of cells or embryos into *any and all species* of surrogate hosts. The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether one of skill in the art could determine "which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." (MPEP §2164.8(b); Atlas Powder Co. v. duPont, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976)). As discussed below, at the time the instant application was filed and before, those of skill in the art knew how to select suitable host surrogates for development of transgenic animals through interspecies embryo or cell transfer.

The Patent Office has acknowledged that the claims are enabled for the claimed methods where the cell develops into an embryo in a female non-human mammal *of the same species*. As discussed below, a consideration of the factors recited in Ex parte Forman leads to the conclusion that it would not require undue experimentation to produce transgenic non-human mammals containing satellite artificial chromosomes by introducing a cell containing a satellite artificial chromosome into a female non-human mammal, where the cell develops into an embryo in the female non-human mammal of *different species* from the embryo, and the embryo further develops into a transgenic non-human mammal containing a satellite artificial chromosome.

2) The state of the art for implantation of embryos into surrogate mothers of different species is **not** unpredictable.

The Examiner cites Fehilly *et al.* (1984) *Nature* 307:634-636 in support of the allegation that implantation of embryos from foreign species into a surrogate mother is "unpredictable."

It is respectfully submitted that the teachings of the specification, when combined with the knowledge of those of skill in the art as of the effective filing date of the instant application, demonstrate that the methods of embryo transfer and implantation into a surrogate of the same species or of a different species are the same, as is the successful generation of transgenic animals therefrom. Therefore, generation of a transgenic animal by implantation of an embryo or cell into a suitable host surrogate of any species was predictable at the time the instant application was filed.

Further, contrary to the Examiner's assertion that Fehilly *et al.* teaches the unpredictability of interspecies implantation, Applicant respectfully submits that this reference demonstrates that as of its publication in 1984, it was possible for one skilled in the art to produce live offspring from embryos implanted into a surrogate female of another species. Each experiment of Fehilly *et al.* produced full-term, live birth off-spring. As shown in Table 1 (page 635), lamb off-spring were carried by goat mothers, kid off-spring were produced by female sheep and interspecific chimeras were produced in surrogates of both species. Further, the results of Fehilly *et al.* demonstrate that cells from both goats and sheep are capable of developing into transgenic animals when implanted in a female surrogate of a different species. The authors also state that "they [interspecific blastocysts] were as viable as intraspecific embryos of the same cell number, whether chimaeric or non-chimaeric" (page 635, col. 1, ¶3).

Additionally, the work of Fehilly *et al.* demonstrates that implantation of embryos goes beyond interspecies transfer, as goat and sheep represent different genus of mammals. Thus, Fehilly *et al.* demonstrates that implantation of embryos into a female surrogate of a different genus was known and available to those of skill in the art as of 1984. The success of Fehilly *et al.* is further corroborated by the publication of Dixon (1984) *Hastings Cent. Rep. 14*:10-12, which describes the efforts of Fehilly *et al.* (referred therein as Dr. Tucker and her collaborators) as surmounting the previous incompatibility problems experienced between different

species and genus. Dixon states: "The breakthrough is knowledge of how to persuade one genus of animal to carry to term a fetus of another species" (page 12, ¶2).

Numerous additional references support the use of methods of embryo transfer as described in the specification for successful interspecies implantation and surrogacy. As the instant specification describes, embryo transfer involves the implantation of an embryo or cells that will form an embryo within the female reproductive tract and maintenance to term (see for example page 34, lines 18-24, and also page 107, lines 16-21) and such transfer was known in the art and successfully used in interspecies transfer as of the effective filing date.

For example, Kraemer *et al.* (1983) *Experimental Zoology 228*:363-371) describes many interspecific transfers that resulted in live births and off-spring. The representative embryos and surrogate females cover a wide variety of species and genus: *Bos taurus* into *B. indicus*, *Bos gaurus* into *B. taurus*, *Ovis musimon* into *O. aries*, *E.caballas* into *E.asinum*, horse into a mare mule, and *Peromyscus maniculatus* into *P. lucipus* (abstract, page 363, and on page 369, col. 2, ¶3 and 4). A number of additional successful interspecies transfers had been demonstrated as of the effective filing date of the instant application. For example, Dresser (1989) *Cat News Issue 11 (19)* and Pope *et al.* (1993) *J. Reprod Fertil Suppl. 47*:189-201 each describe interspecies transfer of embryos between cat species, for example, a *Felis silvestria ornata* (Indian desert cat) embryo implanted in a domestic house cat surrogate developed to term and was born in the Cincinnati Zoo Feb 7, 1989. Summers *et al.* (1984) *Aust. J. Exp. Biol. Med. Sci. 62*:27-45 demonstrates the successful production of *Bos taurus* and *Bos indicus* chimeric and non-chimeric calves in both *Bos taurus* and *Bos indicus* surrogate females, including 22 pairs of interspecies twin calves birthed (see for example, page 29, ¶1 and Table 1, page 33). Rorie *et al.* (1994) *Veterinary Record 135*:186-187 describes a simplified procedure for both interspecific and intergeneric embryo transfers and demonstrates successful transfer and live birth

of lambs from goat surrogate females (see, for example, page 187 ¶¶ 2-3). Rossant *et al.* (1980) *Science 208*:419-421 demonstrates the successful transfer of interspecific chimeras of *mus musculus* and *mus caroli* carried to term in the female *mus musculus*. The publications of Kraemer *et al.*, Dresser, Pope *et al.*, Summers *et al.*, Rorie *et al.* and Rossant *et al.* each demonstrate the successful interspecies and intergeneric species development of embryos and cells in animals, carried to term and born live in female surrogates of the same or different species or a different genus. Further, these references demonstrate success in a wide variety of animal species including sheep, goat, cat, mouse and cattle.

In addition to the above, to evidence that the methods as claimed operate as claimed, provided in a Supplemental Information Disclosure Statement filed under separation cover are references (Lanza *et al.* (2000) *Scientific Amer. Nov*:85-89; Woods *et al.* (2003) *Sciencexpress* published online May 29 2003; Press Releases of Advanced Cell Technology dated January 12, 2001 and April 8, 2003; and Loi *et al.* (2001) *Nat. Biotechnol. 10*:962-4) demonstrating operability of such methods. These publications (provided to demonstrate operability not enablement) show that by following the teachings of the application and what was known to those of skill in the art at the effective filing date of the instant application, embryo transfer into female surrogates of a different species permits the generation of transgenic animals. Although post-filing date references, they evidence that the methods as provided and claimed in the instant application function as claimed and that **no additional information beyond the teachings in the specification and knowledge of those of skill in the art at the time of the effective filing date of the instant application is required** to perform the methods as claimed. The specification teaches how to use the ACs to produce transgenic animals; such use does not require that the host animal be the same species as the embryo.

The reference Lanza *et al.* (2000) *Scientific Amer. Nov*:85-89 demonstrates that live transgenic animals are produced by embryo transfer into surrogate females of different species. This reference describes the operability of

interspecies implantation of the African wildcat into a housecat, gaur into cow, a mouflon into a sheep and a red deer into a common white-tailed deer (page 86, col. 3, last paragraph). Further, although this is a post-filing reference, Lanza *et al.* cites an example of a successful interspecies transfer prior to the effective filing date of the instant application, a bongo embryo into a surrogate eland antelope, resulting in the successful birth of the bongo in 1984 (page 87, paragraph bridging columns 2 and 3).

Woods *et al.* demonstrates the successful cloning of a mule (*Equus asinus*) after implantation of embryos into a mare (*Equus caballus*) and the live birth of a developmentally normal foal. The press releases from Advanced Cell Technology (Worster, MA) describe the live birth of a gaur after implantation and development in a surrogate cow female in 2001 and the live birth of two banteng off-spring in 2003 from the implantation of the banteng embryos into domestic cow surrogates. Loi *et al.* describes the cloning from *Ovis orientalis* (mouflon) oocytes by transfer of the cells into a surrogate *Ovis aries*, producing live normal mouflon in 2001. These references demonstrate that by following the methods of the instant application, a cell/embryo of one species can develop into a transgenic animal by implantation into a female non-human mammal of a different species.

Thus, in summary, the record clearly demonstrates that interspecies transfer was known to and demonstrated by those of skill in the art as of the time of filing of the instant application as evidenced by the publications of Fehilly *et al.*, Kraemer *et al.*, Dresser, Pope *et al.*, Summers *et al.*, Dixon, Rorie *et al.* and Rosant *et al.*. Each of the aforementioned references demonstrate that interspecies transfer resulted in successful pregnancies carried full term and the delivery of live birth off-spring. Additionally, the operability of such methods in the production of animals from interspecies transfers is evidenced by the publications of Lanza *et al.*, Woods *et al.*, Advanced Cell Technology Press Releases and Loi *et al.*

3) Consideration of the factors that determine whether the application provides sufficient guidance as to enable the subject matter of the claims leads to the conclusion that the amount of experimentation required by one of skill in the art to practice the claimed subject matter is **not** undue.

As discussed above, the standard for enablement is whether it would require undue experimentation to practice the methods as claimed. A determination of the amount of experimentation that is permissible and not undue depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986).

It is respectfully submitted that in view of the breadth of the claims, the level of skill in the art, the knowledge of those of skill in the art, the teachings and disclosure in the specification regarding methods for generating cells with satellite artificial chromosomes, methods of introducing exogenous DNA such as satellite artificial chromosomes into cells, methods of developing cells into an embryo, methods of implanting cells and embryos in a surrogate female, selection of suitable host surrogates for implantation of cells and embryos that develop into transgenic animals, including surrogates of different species, and methods of generating a transgenic animal from such cells or embryos, and the predictability of such methods, undue experimentation is not required to perform the methods of the instant application where the species of the surrogate and embryo differ.

As demonstrated below, the level of knowledge and skill in the art for introduction of exogenous DNA into cells and the production of transgenic animals from such cells was sufficiently high as of the effective filing date of the claimed subject matter that it would not have required extensive experimentation by one of skill to produce transgenic animals containing a satellite artificial chromosome by the methods as taught and exemplified by working examples in the specification, and the publications incorporated therein by reference. Furthermore, as is

discussed below, the level of knowledge and skill in the introduction of cells and embryos into female surrogates was sufficient as of the effective filing date, including knowledge and skill in the implantation and development of cells and embryos in surrogates of different species, such that it would not have required undue experimentation for one of skill in the art to produce transgenic animals containing a satellite artificial chromosome in a female surrogate of another species.

The specification describes methods for generation of cells with satellite artificial chromosomes that are capable of developing into embryos, and exemplifies such methods with respect to the development of transgenic mice. There is **no** evidence of record that suggests that such methods are unique to cells and embryos that are of the same species as the female surrogate into which they are introduced for development into a transgenic animal. To the contrary, the specification in light of the level of skill in the art teaches that each of the aforementioned steps and the methods based thereon are applicable to any species and this is further supported by the knowledge of those of skill in the art as of the effective filing date of the instant application.

Scope of the claims

The claims are directed to methods of producing transgenic animals in which a satellite artificial chromosome is introduced into a cell and the cell containing the satellite artificial chromosome develops into a transgenic animal or embryo. Independent claim 32 is directed to a method of producing a transgenic non-human mammal that includes: introducing a cell comprising a satellite artificial chromosome, wherein the cell develops into an embryo in a female non-human mammal, and allowing the embryo to develop into a transgenic non-human mammal comprising the satellite artificial chromosome. Independent claims 97-100 are directed to similar methods of producing a transgenic non-human mammal using embryos, fertilized oocytes, an ovum or mouse embryonic stem (ES) cells containing satellite artificial chromosomes. Dependent claims further specify cell

types, types of satellite artificial chromosomes, pronuclear localization of the satellite artificial chromosome, and methods of introducing a satellite artificial chromosome into a cell. Added claims 111 and 112 are directed to the method of claim 32 or claim 97, respectively, where the embryo and the female non-human mammal are of the same species.

Independent claim 82 and claims 83 and 87 dependent thereon are directed to a method of producing a transgenic embryo by introducing a satellite artificial chromosome into a cell and culturing the cell under conditions where it develops into an embryo. These claims do not recite implantation of the embryo for "developing in a female non-human mammal" and therefore do not appear to be within the purview of this rejection.

Claims 106 and 107, which are not specified as being within the purview of this rejection, are directed to a method for producing a transgenic non-human mammal in which an ovum containing a satellite artificial chromosome is introduced into a female non-human mammal where it develops into a zygote or embryo, and the zygote or embryo is further allowed to develop into a transgenic non-human animal containing the satellite artificial chromosome.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the specification

The specification describes the production of transgenic mammals containing satellite artificial chromosomes, generating cells with satellite artificial chromosomes, generating embryos with satellite artificial chromosomes, the transplantation of cells and embryos into recipient females and their subsequent development into a transgenic animal. Each of these steps are described in detail in the specification. In addition, the specification provides numerous working

examples of the procedures and results involved in the claimed methods. For example, the specification discloses methods for generating cells with satellite artificial chromosomes that include methods for the generation of satellite artificial chromosomes and their delivery into cells; the introduction of satellite artificial chromosomes into cells that form zygotes or embryos; the implantation of the zygote or embryo into a surrogate female; the development of the implanted cells or embryo or zygote into an animal; and the generation of a transgenic animal containing a satellite artificial chromosome.

The specification describes the generation of artificial chromosomes that can be used in the instantly claimed methods. For example, at pages 24-27, the specification details methods for the preparation of satellite artificial chromosomes. Additional detailed methods are provided in Figures 2 and 4 of the specification. Methods for isolating satellite artificial chromosomes which then allow transfer of satellite artificial chromosomes to other cell lines are found for example, at page 30, line 27 through page 31, line 7. Such methods are exemplified in Example 7, pages 66-68, which describes cell lines generated with satellite artificial chromosomes and Example 10, pages 78-81, which exemplifies methods for purification of artificial chromosomes which can then be used to generate other cell types with satellite artificial chromosomes.

The specification describes methods of generating cells containing satellite artificial chromosomes by transferring satellite artificial chromosomes into cells using methods such as microinjection (page 34, lines 18-19), and numerous other delivery methods such as direct DNA uptake, electroporation, lipofection, cell fusion and particle bombardment (page 31, lines 14-24 and page 34, line 25 through page 35, line 3). Methods are taught for microinjection into embryonic cell lines (page 32, lines 3-11). Methods using calcium phosphate and polyethylene glycol for DNA uptake into mammalian cells also are taught (page 32, lines 16-21). These methods also are described in detail for example, in Example 1 (cell fusion and microcell fusion, page 41, line 25 through page 42, line 21). Further, Example

13 (pages 103-106) exemplifies the use of microinjection to introduce an artificial chromosome into mammalian cells. Microinjection into embryos and ES cells is described in detail in Example 14 (page 106, line 5 through page 107, line 21; page 109, lines 13-24; page 110, lines 3-10) as well as the use of cell fusion and microcell procedures for transferring an artificial chromosome into ES cells and embryonic stem cells (page 110, lines 11-27).

The specification describes the introduction of satellite artificial chromosomes into cells capable of developing into embryos such as embryonic stem cells (page 32, lines 3-8) and zygotes (page 34, lines 18-19). The specification describes microcell fusion and cell fusion methods for use with embryonic stem cells (page 81, lines 26-30 and page 110, lines 11-27). Microinjection into zygotes is exemplified in Example 14 (page 109, lines 13-21).

The development of cells into embryos and the development of cells and embryos into animals are described. For example, the specification describes the microinjection of zygotes, the implantation of zygotes into a host female uterus and the subsequent development of the zygote into a mammal (page 34, lines 18-24). Example 14 exemplifies the development of embryos in culture and the implantation into surrogate females (page 107, lines 16-21), and the implantation of microinjected zygotes into surrogate female mice and their development into transgenic offspring (page 109, lines 21-23). Additionally, Example 14 describes methods for transplanting stem cells with satellite artificial chromosomes into mouse blastocysts and their subsequent development into a transgenic mouse (page 110, lines 22-27).

Knowledge of those of skill in the art

At the time of filing of the application, a broad body of knowledge had amassed in the area of generating cells with exogenous DNA and generating transgenic animals from such cells. Numerous procedures related to these areas are cited in the application.

The specification cites numerous references for generating cells containing exogenous DNA such as satellite artificial chromosomes. At page 31, lines 21-24, the specification cites methods for transforming mammalian cells such as Keown *et al. Methods in Enzymology* (1990) Vol. 185, pp. 527-537; and Mansour *et al.* (1988) *Nature 336*:348-352. The specification cites Hogan *et al.* (1994) *Manipulating the Mouse Embryo: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor as an example of microinjection techniques (page 32, lines 5-8), Graham *et al.* (1978) *Virology 52*:456-457 as an example of calcium phosphate delivery methods (page 32, line 18), electroporation techniques such as those provided in U.S. Patent Nos. 4,784,737, 5,501,967, 5,501,662, 5,019,034, 5,503,999 and Fromm *et al.* (1985) *Proc. Natl. Acad. Sci. U.S.A.* 82:5824-5828 (page 33, lines 5-9), and microcell techniques such as those provided in U.S. Patent Nos. 5,240,840, 4,806,476, 5,298,429, Fournier (1981) *Proc. Natl. Acad. Sci. U.S.A. 78*:6349-6353; and Lambert *et al.* (1991) *Proc. Natl. Acad. Sci. U.S.A. 88*:5907-59 (page 33, lines 23-28).

The specification references methods of generating transgenic animals from introduced cells. For example, at page 34, lines 20-22, the specification cites U.S. Patent Nos. 4,873,191 and 5,354,674, International PCT application No. WO95/14769 and U.S. application Serial No. 08/159,084 in reference to techniques of zygote microinjection and the production of transgenic mammals. The specification further cites Hogan *et al.* (1994) *Manipulating the Mouse Embryo: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (especially pages 255-264 and Appendix 3) for techniques of cell culture, implantation and development of transgenic animals in a surrogate female (page 106, line 31 through page 107, line 2).

The numerous references to published protocols and procedures for generating cells containing exogenous DNA and generating transgenic animals from such cells, demonstrate the large volume of information that was available at the time of filing of the instant application and thus evidence the advanced state of

the art at the relevant time. The specification details their application to the claimed and disclosed methods.

Further, as discussed in the response filed January 10, 2003, to the Office Action of July 20, 2002, numerous books and articles available at the effective filing date of the instant application detail various procedures for the generation of transgenic animals using implantation of cells into female animals (see, *e.g.*, "Animals with Novel Genes", Maclean (Ed.), Cambridge University Press, 1994; "Transgenic Animal Technology", Pinkert (Ed.), Academic Press, 1994; Capecchi, "Targeted Gene Replacement", *Sci. American 270(3)*: 52-59 (1994); Bondioli "Nuclear Transfer in Cattle" *Mol. Reprod. Dev. 36*: 274-275 (1993); Kaufman *et al.* "Handbook of Molecular and Cellular Methods in Biology and Medicine" CRC Press, pp. 357-365 (1995); Fässler *et al.* "Knockout Mice: How to Make Them and Why. The Immunological Approach" *Int. Arch. Allergy Immunol. 106*: 323-334 (1995); Campbell *et al.* (1996) *Nature 380*:64-66; and PCT Application Publication No. WO 95/17500).

Furthermore, as discussed above and below when addressing predictability of the claimed methods, interspecies implantation of embryos in a wide variety of species was known as of the effective filing date of the instant application. For example, Kraemer *et al.* (1983) *Experimental Zoology 228*:363-371) describes inter-species specific embryo transfer in a large number of species such as rabbit, rat, sheep, mouse, goat, cattle, pig, hamster, ferret, mink, horse, primates, cat, dog and water buffalo. Additional examples of inter-species specific embryo transfer, discussed above and below, are described in Dresser (1989) *Cat News Issue 11 (19)*; Pope *et al.* (1993) *J. Reprod Fertil Suppl. 47*:189-201; Summers *et al.* (1984) *Aust. J. Exp. Biol. Med. Sci. 62*:27-45; Rorie *et al.* (1994) *Veterinary Record 135*:186-187; and Rossant *et al.* (1980) *Science 208*:419-421. As is shown by these references, the methods of embryo transfer and implantation known and available to those of skill in the art at the time the instant application was filed allowed for selection of a suitable host of any species for development of

an animal from cells or embryos of a different species. Thus, at the time the instant application was filed and before, those of skill in the art knew how to select suitable host surrogates that were operative and for development of transgenic animals through interspecies embryo or cell transfer. The numerous publications known to those of skill in the art prior to the effective filing date of the instant application demonstrate the successful development of cells and embryos into animals when implanted into female surrogates of different species.

Presence of working examples

The specification provides numerous working examples and descriptions of the generation of satellite artificial chromosomes, the generation of cells containing satellite artificial chromosomes, the generation of cells containing satellite artificial chromosomes that are capable of developing into an embryo, the development of cells into embryos and the subsequent development of an embryo into a transgenic animal. As described above, Example 7, pages 66-68, exemplifies the generation of cell lines containing satellite artificial chromosomes and Example 10, pages 78-81, exemplifies methods for purification of artificial chromosomes which can then be used to generate additional cell types containing satellite artificial chromosomes. Example 1 exemplifies cell fusion and microcell fusion (page 41, line 25 through page 42, line 21). Example 13 (pages 103-106) and Example 14 (page 106, line 4 through page 107, line 21; page 109 lines 13-24; page 110, lines 3-10) exemplify the use of microinjection and Example 14 in particular, exemplifies methods for introducing artificial chromosomes into zygotes and embryonic stem cells. Example 14 also exemplifies the development of embryos in culture and the implantation into surrogate females (page 107, lines 16-21), the implantation of microinjected zygotes into surrogate female mice and their development into transgenic offspring (page 109, lines 21-23).

Predictability

As discussed above and as known to those of skill in the art, the level of knowledge and skill in the generation of cells containing exogenous DNA and their use in methods of generating transgenic animals as instantly claimed was high as of the effective filing date. Therefore, given the extensive teachings of the specification, in combination with what was known to those of skill in the art at the time the instant application was filed, it is not unpredictable that the methods provided in the instant application can be used with cells or embryos that develop in a suitable surrogate female host of a different species. Furthermore, the outcome of such implantation is not unpredictable.

The pending claims are directed to methods of producing a transgenic non-human mammal by introducing a cell containing a satellite artificial chromosome into a female non-human mammal such that the cell develops into an embryo in the female non-human mammal, and allowing the embryo to develop into a transgenic non-human mammal containing the satellite artificial chromosome.

The Office Action cites Fehilly *et al.* (1984) *Nature* 307:634-636 as an example of the unpredictability of implantation of embryos from foreign species into a surrogate mother. First, it is respectfully submitted that any broad sweeping assertions as to the difficulties in carrying a live hybrid fetus to term based on Fehilly *et al.*, published in 1984, bear little or relevance to the issue of whether or not the instant application filed June 12, 1998, as a continuation of an application filed April 10, 1996, is enabled for the methods it teaches and claims. As the discussion herein demonstrates, by 1996, the relevant art had advanced significantly since 1984.

Further, as discussed above, Fehilly *et al.* in fact demonstrates the predictability of interspecies implantation. Each experiment of Fehilly *et al.* showed that as of its publication in 1984, full-term, live birth off-spring could be produced by interspecies embryo transfer.

Furthermore, as also discussed above, in addition to Fehilly *et al.*, interspecies implantation of embryos was known in a wide variety of species as of the effective filing date of the instant application. For example, Kraemer *et al.* (*supra*) describes many interspecific transfers that resulted in live births and off-spring. The representative embryos and surrogate females cover a wide variety of species and genus: *Bos taurus* into *B. indicus*, *Bos gaurus* into *B. taurus*, *Ovis musimon* into *O. aries*, *E.caballas* into *E.asinum*, horse into a mare mule, and *Peromyscus maniculatus* into *P. lucipus* (abstract, page 363, and on page 369, col. 2, ¶3 and 4). A number of additional successful interspecies transfers had been demonstrated as of the effective filing date of the instant application. For example, Dresser (1989) *Cat News Issue 11 (19)* and Pope *et al.* (1993) *J. Reprod Fertil Suppl. 47*:189-201 each describe interspecies transfer of embryos between cat species, for example, a *Felis silvestria ornata* (Indian desert cat) embryo implanted in a domestic house cat surrogate developed to term and was born in the Cincinnati Zoo Feb 7, 1989. Summers *et al.* (1984) *Aust. J. Exp. Biol. Med. Sci. 62*:27-45 demonstrates the successful production of *Bos taurus* and *Bos indicus* chimeric and non-chimeric calves in both *Bos taurus* and *Bos indicus* surrogate females, including 22 pairs of interspecies twin calves birthed (see for example, page 29, ¶1 and Table 1, page 33). Rorie *et al.* (1994) *Veterinary Record 135*:186-187 describes a simplified procedure for both interspecific and intergeneric embryo transfers and demonstrates successful transfer and live birth of lambs from goat surrogate females (see, for example, page 187 ¶¶ 2-3). Rossant *et al.* (1980) *Science 208*:419-421 demonstrates the successful transfer of interspecific chimeras of *mus musculus* and *mus caroli* carried to term in the female *mus musculus*.

In addition, to evidence that the methods as claimed operate as claimed, provided in a Supplemental Information Disclosure Statement filed on the same day herewith are publications (Lanza *et al.* (2000) *Scientific Amer. Nov*:85-89; Woods *et al.* (2003) *Sciencexpress* published online May 29 2003; Press Releases of

Advanced Cell Technology dated January 12, 2001 and April 8, 2003; and Loi *et al.* (2001) *Nat. Biotechnol. 10*:962-4) demonstrating that by following the teachings of the application and what was known to those of skill in the art at the effective filing date of the instant application, embryo transfer into female surrogates of a different species permits the generation of transgenic animals according to the instantly claimed methods.

As discussed above, although these publications rebut assertions of inoperativeness, they also further evidence enablement. It is noted that the level of skill in the biotechnical arts is recognized to be high (see, *e.g.*, *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986). Further, as discussed, methods for performing the various steps of the claimed methods, such as generating cells with exogenous DNA and their use in generating transgenic animals are known to the skilled artisan.

As discussed above, the reference Lanza *et al.* (2000) *Scientific Amer. Nov*:85-89 describes the operability of interspecies implantation of the African wildcat into a housecat, gaur into cow, a mouflon into a sheep and a red deer into a common white-tailed deer (page 86, col. 3, last paragraph). Lanza *et al.* also cites an example of a successful interspecies transfer prior to the effective filing date of the instant application, a bongo embryo into a surrogate eland antelope, resulting in the successful birth of the bongo in 1984 (page 87, paragraph bridging columns 2 and 3).

Woods *et al.* demonstrates the successful cloning of a mule (*Equus asinus*) after implantation of embryos into a mare (*Equus caballus*) and the live birth of a developmentally normal foal. The press releases from Advanced Cell Technology (Worster, MA) describe the live birth of a gaur after implantation and development in a surrogate cow female in 2001 and the live birth of two banteng off-spring in 2003 from the implantation of the banteng embryos into domestic cow surrogates. Loi *et al.* describes the cloning from *Ovis orientalis* (mouflon) oocytes by transfer of the cells into a surrogate *Ovis aries*, producing live normal mouflon in 2001.

Thus, the record clearly demonstrates that interspecies transfer was known to and demonstrated by those of skill in the art at the time of filing of the instant application as evidenced by the publications of Fehilly *et al.*, Kraemer *et al.*, Dresser, Pope *et al.*, Summers *et al.*, Dixon, Rorie *et al.* and Rosant *et al.*. Each of the aforementioned references demonstrate that interspecies transfer resulted in successful pregnancies carried full term and the delivery of live birth off-spring. Additionally, the operability of such methods in the production of animals from interspecies transfers is evidenced by the publications of Lanza *et al.*, Woods *et al.*, Advanced Cell Technology Press Releases and Loi *et al.* Thus, there is no evidence of record that interspecies transfer for the successful generation of transgenic animals was not predictable as of the effective filing date of the instant application.

It appears that the Office Action, in asserting the unpredictability of interspecies implantation has equated "limitations" with "unpredictability." It is respectfully submitted that although certain limitations of interspecies implantation may exist, this does not establish the art as unpredictable. Moreover, the limitations pointed to by the Examiner have no bearing on enablement of the methods as claimed.

For example, the Examiner cites "low percentage of full term young" obtained according to the methods of Fehilly *et al.* as evidence of "unpredictability" of interspecies transfer. Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for an area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, method; rather, even in an *unpredictable* art, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill in the art how to make and use the claimed

subject matter without undue experimentation. The teachings of Fehilly *et al.* support the teachings of the specification and the knowledge of those of skill in the art at the time the instant application was filed, demonstrating that the methods as instantly claimed can be used to produce live-born transgenic animals by interspecies embryo or cell transfer.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable that cells or embryos from one species can be implanted into a female surrogate host of a different species for the generation of transgenic animals and the breadth of the claims, it would not require undue experimentation for one of skill in the art to practice the methods as claimed.

Accordingly, a consideration of the factors enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to introduce a cell of embryo into a female non-human host mammal for generation of a transgenic animal therefrom, where the female non-human host mammal is of a different species from the implanted cell or embryo.

4) Policy Considerations: It would be unfair and unduly limiting to restrict the scope of the claims as proposed by the Examiner.

As described above, the record demonstrates the successful interspecies transfer and development of cells and embryos in surrogates in a wide variety of different species. Even if there is a possibility that not every interspecies implantation would yield an embryo or animal in a method of transgenic animal production, it would not invalidate a claim that does not specify particular species of cells or surrogates. In re Dinh-Nguyen, 492 F.2d 856 at 858-9, 181 USPQ 46,48 (CCPA (1974)). A claim is not too broad because it does not explicitly exclude possible inoperative applications of a method providing it enables one of skill in the art to practice what is claimed in its workable applications. Thus, what is relevant to the scope of enablement is that there are a number of interspecies implantations and methods known to those of skill in the art based on the

combination of the teachings of the application and what was known in the art at the time of filing of the application, that develop into an embryo and into a transgenic mammal.

Additionally, as is discussed above, a broad body of knowledge was available in the area of interspecies implantation for use in the methods of the instant application for producing transgenic embryos and animals containing satellite artificial chromosomes. Thus it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to intraspecies implantations. See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require Applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. If Applicant is required to limit the claims to only those cells or embryos transferred and developed into transgenic animals in a female of the same species, then those of skill in the art could by virtue of the teachings of this application readily practice what is claimed by substituting the surrogate female with one of a different species or genus in which to practice what is disclosed in the application, but avoid infringing such limited claims.

The Examiner clearly has acknowledged that the steps are enabled where the cell develops into an embryo in a female non-human mammal of the same species. The steps of the methods as claimed are essentially the same whether a female of the same species or of a different species is used (see for example,

Lanza *et al.* and Kraemer *et al.*, *supra*) Thus, the steps of the method as claimed are the same for production of embryos and animals containing satellite artificial chromosomes using either intraspecies or interspecies transfer and these steps are enabled in the instant application. It would therefore be unfair and unduly limiting and contrary to public policy, to limit Applicant to same species when it is known in the art that the steps of the method can be practiced successfully with interspecies production. The instant application provides and exemplifies methods of generating transgenic animals and embryos containing satellite artificial chromosomes. Having done so, it is now routine for others to produce transgenic embryos and animals using these methods. Those of skill in the art should not be permitted to make such minor modifications by substitution of the female surrogate to avoid infringing such claims.

THE REJECTION OF CLAIMS 32, 82 and 109 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 32, 82 and 109 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention because the claims are allegedly unclear in reciting the language "capable of." The Examiner alleges that "capable of" implies a latent property, that conditions for the latent property must be clearly defined and further, it is unclear if the latent property is ever obtained.

Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Claims 32, 82 and 109 are amended to recite that the cell develops into an embryo and dependent claims (35, 38, 39, 65, 100, 108 on claim 32; 83 and 87 on claim 82; 110 on claim 109) incorporate this limitation. Further, claims among these specify that the cell is, *e.g.*, a fertilized ovum or a zygote. Hence, all of the rejected claims encompass cells that develop into embryos.

As discussed in previous responses (mailed February 26, 2002, responsive to the Final Office Action of November 26, 2001; mailed May 26, 2002,

responsive to the Advisory Action of March 18, 2002; and mailed January 10, 2003, responsive to the Final Office Action of July 10, 2002), a variety of cells that develop into embryos and further into transgenic animals may be used in the claimed methods. Exemplary cells for use in the claimed methods are referred to in the application. In addition, in considering the teachings of the specification in combination with transgenic animal production methods known in the art at the time of filing of the instant application, it is clear that one of skill in the art could readily determine a number of cells that develop into embryos and that may be used in the claimed methods. Numerous books and review articles of record that detail various procedures for the production of transgenic animals, including the use of source cell(s), such as embryos, oocytes, zygotes, embryonic stem cells, gametes and germline cells, were known at the time of filing of the instant application (see, *e.g.*, "Animals with Novel Genes", Maclean (Ed.), Cambridge University Press, 1994; "Transgenic Animal Technology", Pinkert (Ed.), Academic Press, 1994; Capecchi, "Targeted Gene Replacement", *Sci. American 270(3)*: 52-59 (1994); Bondioli "Nuclear Transfer in Cattle" *Mol. Reprod. Dev. 36*: 274-275 (1993); Kaufman *et al.* "Handbook of Molecular and Cellular Methods in Biology and Medicine" CRC Press, pp. 357-365 (1995); Fässler *et al.* "Knockout Mice: How to Make Them and Why. The Immunological Approach" *Int. Arch. Allergy Immunol. 106*: 323-334 (1995); Campbell *et al.* (1996) *Nature 380*:64-66; and PCT Application Publication No. WO 95/17500). Therefore, the particular cells that develop into embryos and further into transgenic animals were known to those of skill in the art at the time the instant application was filed and one of skill in the art can combine the teachings of the specification with transgenic animal production methods known in the art at the time of filing and identify what source cell(s) develop into transgenic embryos and non-human mammals.

Because recitation of a cell that "develops" into an embryo does not refer to a latent or uncertain property but rather, as discussed above, to a property that is

adequately defined, Applicant respectfully submits that the claims as amended herein and the claims dependent thereon are not indefinite.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket 24601-402A
Address all correspondence to:
HELLER EHRMAN WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122-1246
Telephone: (858) 450-8400
Facsimile: (858) 587-5360
E-mail: sseidman@HEWM.com